VICH Biological Quality Monitoring WG
Topic: Residual Formaldehyde Testing
Draft Minutes/Action Plan - December 14-15, 1999, Brussels, Belgium

The following summary of issues on the Residual Formaldehyde Draft Guideline, V1.0 were presented:

1. Is it acceptable to limit to one method for a chemical assay?
   - multiple acceptable assay as per *EP/*USP
   - Ferric chloride as the standard assay for government labs, manufacturers method must be standardized against this assay
2. Is ferric chloride the correct assay as the standard assay
   - concern with cost of equipment and hazardous chemicals
3. Are there variations of ferric chloride that are acceptable?
   - microtiter plate method
4. How to standardize and validate procedure(s)?
   - use of standard reference
   - comparison of existing assays

After discussion, it was agreed to insert the following statement in the guideline introduction:

> This document provides a guideline for the general requirements for residual formaldehyde testing. The guideline leaves the flexibility for other testing methods based on the specific scientific situations or characteristics of the target material. These variations must be stated in the manufacturers production method and include equivalence data.

There was considerable discussion on the acceptable levels of residual formaldehyde in final product. The following table is provided to provide clarification as to the units of measure for residual formaldehyde:

g/L formaldehyde	% w/v formaldehyde	% v/v formaldehyde solution*	ppm formaldehyde
2.0	0.2	.5	2000
0.8	0.08	0.2	800
0.4	0.04	0.1	400
0.5	0.05	0.125	500
0.05	.005	0.0125	50
0.04	.004	0.01	40

* based on 40% formaldehyde solution

Based on the above, the limits for free formaldehyde concentrations range from <0.05 g/L in the EU, <0.01 to <0.5%v/v (0.04 – 2.0 g/L) in Japan and <0.2% to <0.5% v/v (0.8 – 2.0 g/L) in the US depending on the type of product. Greater levels are allowed in the EU if supported by host animal safety data. The guideline will be corrected to reflect these units.

It was tentatively agreed that the maximum level of formaldehyde would be 2g/L. This number will be reviewed by the European delegation since this level is 4X higher than the current EU allowable limit without additional supporting safety data.

Safety data was defined as safety in the host animal, paying particular attention to local reactions, with product formulated at approximately the highest level of formaldehyde. This definition was included in the guideline.

It was agreed a two phase testing program should be conducted prior to the next WG meeting, at which time the Residual Formaldehyde Guideline can be finalized.

The first stage study would consist of the distribution of three current commercial products to the three regions. These three products should include:

- An aluminum adjuvanted Clostridial bacterin containing residual formaldehyde levels of >0.8 but less than <2.0 gm/L.
- An oil adjuvanted bacterin containing >0.05 but <0.8 gm/L formaldehyde
- An non-virucidal bacterin (lepto suggested), formalin inactivated, but whose residual formaldehyde concentration has be reduced to <0.05 gm/L by the addition of sodium bisulfate.

Ideally these products should currently be trade in the three regions. USDA will identify the three candidate bacterins based on the response to a Federal Notice. A maximum of 5 industry and government labs from each region (EU/US/Japan and official observer) will be selected by the WG representatives to participate in the study. Each participating lab will test the 3 samples in triplicate by their current assay and the ferric chloride test. Results will be collected by the regional government lab and submitted to the topic leader. These data will show the consistency of testing between regions over a range of residual formaldehyde levels and products.

Phase two would involve the evaluation of a minimum of 5 regional products, in duplicate using both the current regional assay and the ferric chloride assay. These data will demonstrate the utility of the guideline assay for a variety of products, and provide preliminary date on the consistency of the assay over a variety of products.

Data for these two studies will be used to suggest the scope of future equivalence and validation studies. The topic leader will prepare a study outline before December 3, 1999.

The following timeline was agreed to:

1. Prepare Federal Notice for vaccine identification – November 29
2. Circulate minutes, final guideline draft and experimental designs - December 3
3. Identify candidate vaccines, finalize experimental design - Dec 17
4. Complete experimental studies - May 31
5. Data compilation/evaluation - July 3
6. Final guidelines – following mid-July WG meeting